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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,043	10/13/2005	Xin Lu	5585-69856-01	6728

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,043	LU ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8,11-14,57,58 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8, 11-14, 57, 58, and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The finality of the previous Office action is hereby withdrawn. The Amendments and Remarks filed 4/2/08 in response to the Office Action of 3/26/08 are acknowledged and have been entered.

Claims 1-3, 8, 11-14, 57, 58, and 60 are pending and are currently under examination.

The indicated allowability of claims 1-3, 8, 11-14, 57, 58, and 60 is withdrawn in view of NEW GROUNDS of rejections necessitated by New Considerations.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8, 11-14, 57, 58, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of nucleic acid molecules encoding polypeptides wherein the amino acid sequence of said polypeptides consist of a sequence that has at least 95% sequence identity with residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 and wherein the polypeptide inhibits apoptotic activity of p53.

The specification discloses the polypeptide set-forth as SEQ ID NO:8 inhibits the apoptotic function of p53 (page 2, in particular). The specification further discloses particular fragments of the polypeptide set-forth as SEQ ID NO:8 that enhance apoptosis (page 38, in particular), presumably by blocking the inhibitory activity of the complete polypeptide set-forth as SEQ ID NO:8. It is noted that said fragments consist of particular regions found outside of residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 (see Figure 10, in particular). However, the specification does not provide any working examples demonstrate that any polypeptides consisting of a sequence that has at least 95% sequence identity with residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 inhibit apoptotic activity of p53. Further, based on the ability of polypeptide fragments of SEQ ID NO:8 to enhance apoptosis, one of skill in the art would not expect polypeptide fragments of SEQ ID NO:8 encoded by the claimed polynucleotides to inhibit apoptosis. Further, if after performing experimentation to demonstrate that a polypeptide encoded by a claimed polynucleotide inhibits apoptosis, undue experimentation would be required to determine which variants would also inhibit apoptosis.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by

nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of polynucleotides that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is likely highly variant, the disclosure of the polypeptide set-forth as SEQ ID NO:8 is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Further, in regards to a genus encompassing variants characterized by encoding a polypeptide having an activity, Applicant is directed to Example 11 of the Written Description Training Materials (http://www.uspto.gov/web/menu/written.pdf), which addresses claims drawn to a genus of polypeptide variants that have activity X. Example 11 states that even when a specification discloses that changes which produce variants are routinely done in the art, the specification or the claims must provide guidance as to precisely what changes should be made. Structural features

that distinguish the compounds of the claimed genus from others not encompassed by the genus are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is needed. General knowledge in the art includes knowledge that some amino acid variations are tolerated without losing a protein's structure. Therefore, given what is known in the art about likely outcome of substitutions on structure, those in the art would have likely expected the Applicant to have been in possession of a genus nucleic acid molecules encoding polypeptides wherein the amino acid sequence of said polypeptides consist of sequence having tertiary structure similar to a polypeptide consisting of residues 128-224 of the amino acid sequence presented in SEQ ID NO:8; however, the claim is not so limited. Those of skill in the art would recognize that conservation of structure is not necessarily a surrogate for conservation of function. For example, Burgess *et al.* (J. Cell Biol. 111:2129-2138, 1990) shows that a conservative replacement of a single "lysine" residue at position 118 of acidic fibroblast growth factor by "glutamic acid" led to a substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar *et al.* (Mol. Cell Biol. 8:1247-1252, 1998) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 alone with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or what appears to be an

inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-3, 8, 11-14, 57, 58, and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabled for making or using nucleic acid molecules encoding polypeptides wherein the amino acid sequence of said polypeptides consist of a sequence that has at least 95% sequence identity with residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 and wherein the polypeptide inhibits apoptotic activity of p53. Further, the specification is not enabled for making or using isolated and non-isolated cells comprising the polynucleotides of claims 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to nucleic acid molecules encoding polypeptides wherein

the amino acid sequence of said polypeptides consist of a sequence that has at least 95% sequence identity with residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 and wherein the polypeptide inhibits apoptotic activity of p53. Further, the claims encompass isolated and non-isolated cells comprising the polynucleotides of claims 1.

The specification discloses the polypeptide set-forth as SEQ ID NO:8 inhibits the apoptotic function of p53 (page 2, in particular). The specification further discloses particular fragments of the polypeptide set-forth as SEQ ID NO:8 that enhance apoptosis (page 38, in particular), presumably by blocking the inhibitory activity of the complete polypeptide set-forth as SEQ ID NO:8. It is noted that said fragments consist of particular regions found outside of residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 (see Figure 10, in particular). Further, the specification does not provide any working examples demonstrating that any polypeptides consisting of a sequence that has at least 95% sequence identity with residues 128-224 of the amino acid sequence presented in SEQ ID NO:8 inhibits apoptotic activity of p53. Further, the specification discloses polynucleotide constructs disclosed therein can be introduced into isolated cells at page 8. Furthermore, the specification discloses the claimed polynucleotides can be incorporated in vivo into cells of multicellular eukaryotic animals (page 13, in particular).

The lack of a written description for said polynucleotides is discussed above. Without such a written description, one would not be able to make or use said polynucleotides without undue experimentation.

Further, the specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use cells that are comprised within a non-human transgenic animal. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. Houdebine (*Journal of Biotechnology* 1994, 34: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions. Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable. Therefore, it is concluded that one of skill in the art would need to perform undue experimentation in order to make and use the claimed host comprised within a transgenic animal.

In addition, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing host cells within a living organism, which comprise the polynucleotides of the instant claims, transformed or transfected by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, 389: 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, 2: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; 1 (1): 122-134) in the abstract. Pandha et al. teach:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues.

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and

exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

/MISOOK YU/

Primary Examiner, Art Unit 1642